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(57) Abstract

Aqueous caffeine solutions containing a co-solubilizing agent selected from niacinamide, nicotinic acid and mixtures thereof present at a level up to the maximum concentration soluble in water and in a weight ratio to caffeine less than 1.50:1, wherein the caffeine is present up to the maximum level between about 2 and about 20 percent by weight that is water-soluble in combination with the co-solubilizing agent and the solution is buffered to a pH less than about 6. Methods for preparing the aqueous caffeine solutions of the present invention are also disclosed.

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AQUEOUS CAFFEINE DOSAGE FORMS

TECHNICAL FIELD

The present invention relates to caffeine dosage forms prepared as aqueous solutions of high levels of caffeine buffered to a pH at which the taste of the caffeine can be effectively masked. In particular, the present invention relates to the use of niacinamide and nicotinic acid as caffeine co-solubilizing agents to provide high concentration caffeine solutions with improved taste that are capable of being effectively formulated with taste-masking components. The present invention also relates to methods for making the buffered caffeine solutions.

BACKGROUND ART

Oral caffeine dosage forms are desirable for use as over-the-counter stimulants that can be prepared in the form of breath sprays or breath drops. As a central nervous system stimulant, the administration of caffeine in combination with analgesics and topical anesthetics increases the analgesic or anesthetic effect. Therefore, aqueous oral dosage forms of caffeine with these ingredients would be desirable to provide a product for the temporary relief of toothache or gum inflammation until a dental professional could be consulted.

Caffeine, however, has limited water solubility. This is evident from U.S. Patent No. 5,382,436, which discloses topical caffeine compositions for use in the treatment of Herpes virus infections. From 8 to 12 percent by weight of caffeine is applied in the form of a dispersion in a topical excipient. This is but one known end-use application for which aqueous caffeine solutions of higher concentration would be desirable.

The acid addition salts of caffeine with citric or hydrochloric acid have significantly greater water solubility. However, the acid addition salts also have an unpleasant taste that is virtually impossible to mask in a commercially practical manner.

Unpleasant tastes are ordinarily masked with an artificial sweetener such as aspartame in combination with flavoring agents. However, solutions of caffeine hydrochloride and caffeine citrate at dosage-effective concentrations have pH's far too low, typically 2.0 and lower. The solutions cannot even be buffered for compounding with aspartame and flavoring agents, which are hydrolytically unstable at these pH's and degrade to reveal the unpleasant taste of the caffeine acid addition salt solution.

There exists a need for higher concentration caffeine solutions in water at pH's acceptable for formulation with taste-masking ingredients.

SUMMARY OF THE INVENTION

This need is met by the present invention. It has now been discovered that caffeine can be co-solubilized with niacinamide and nicotinic acid to form caffeine solutions at dosage-effective concentrations with pH's that can be buffered to a pH at which the taste of the caffeine can be effectively masked. For taste masking to be effective, the pH must be buffered to a pH less than about 6, and preferably less than about 5. For example, the optimum pH for the use of aspartame as a taste-masking agent is about 4.3.

Therefore, in accordance with one embodiment of the present invention, an aqueous caffeine solution is provided containing a co-solubilizing agent selected from niacinamide, nicotinic acid and mixtures thereof present at a level up to the maximum concentration soluble in water and in a weight ratio to caffeine less than 1.50:1,

wherein the caffeine present up to the maximum level between about 2 and about 20 percent by weight that is water-soluble in combination with the co-solubilizing agent, and the solution is buffered to a pH less than about 6.

A pH less than about 5 is preferred, with a pH of about 4.3 being more preferred.

Unexpectedly, folic acid has been found to have significantly increased water-solubility in the caffeine solutions of the present invention. This is desirable, because caffeine is believed to deplete folic acid, an essential B-vitamin, in the body. Therefore, preferred caffeine solutions of the present invention further include folic acid at a level up to the maximum concentration soluble in the caffeine solution. Preferably, the folic acid is present at a level soluble in the caffeine solution up to the amount effective to provide the minimum Recommended Daily Allowance (RDA) of folic acid in a 4.0 mL quantity of the caffeine solution.

Preferred caffeine solutions in accordance with the present invention are also fortified with other essential vitamins, minerals and health food additives. This will influence the choice of a buffering system. Vitamin C, ascorbic acid, is a strong acid that when present at the 50 percent minimum RDA will reduce the pH of caffeine solutions in accordance with the present invention below 4.3. Buffering with a basic system based on sodium bicarbonate, sodium hydroxide, and the like, is necessary. Otherwise, solutions based on caffeine with niacinamide and nicotinic acid and folic acid will produce a pH above 6.0 that requires buffering with an acidulent, preferably one generally regarded as safe, such as citric acid, hydrochloric acid, acetic acid and the like. Nicotinic acid or ascorbic acid may also be used as the acidulent.

Caffeine solutions in accordance with the present invention may also include an analgesic that is capable of being effectively absorbed through the skin or mucous membrane, such as acetylsalicylic acid, acetaminophen, ibuprofen, ketoprofen, menthol and the like. The caffeine solutions of the present invention have unexpectedly been found to promote the water-solubility and effect of topical anesthetics capable of being absorbed through the skin and mucous membranes such as procaine, benzocaine, lidocaine and the like. Therefore, caffeine solutions in accordance with the present invention may further optionally include an analgesic or topical anesthetic capable of being absorbed through the skin or mucous membrane.

The present invention also provides methods by which the aqueous caffeine solutions of the present invention may be prepared. In accordance with this embodiment of the present invention, a method is provided for preparing an aqueous caffeine solution including the steps of:

dissolving caffeine and a co-solubilizing agent selected from niacinamide, nicotinic acid and mixtures thereof in water, so that an aqueous solution of caffeine is formed, wherein the co-solubilizing agent is present at a level up to the maximum concentration soluble in water and in a weight ratio relative to caffeine less than 1.50:1, and the caffeine is present up to the maximum level between about 2 and about 20 percent by weight that is water-soluble in combination with the co-solubilizing agent; and

buffering the caffeine solution to a pH less than about 6.

Without being bound by any particular theory, it is believed that the niacinamide and nicotinic acid function as a

combination co-solubilizing agent that promotes the hydration of the caffeine in water. At higher concentrations, these ingredients may also form water-soluble acid addition salts with the caffeine. Regardless, the co-solubilizing agents effectively provide aqueous caffeine solutions at concentrations greater than 2 percent by weight at a pH that is capable of being buffered to a level at which the taste of the caffeine solution may be effectively masked with artificial flavors and sweeteners. The co-solubilizing agents also provide aqueous caffeine solutions with improved taste compared to the aqueous caffeine addition salt solutions of the prior art, making it simpler to mask the taste of the aqueous caffeine solutions of the present invention.

BEST MODE OF CARRYING OUT THE INVENTION

The aqueous caffeine solutions of the present invention contain caffeine at a level between about 2 and about 20 percent by weight. Aqueous solutions of caffeine up to about 2 percent by weight can be readily prepared without a co-solubilizing agent. For amounts greater than about 2 percent, the level of caffeine employed in the solutions of the present invention will depend upon the co-solubilizing agent selected.

Niacinamide will co-solubilize caffeine solutions up to about 20 percent by weight of caffeine. The amount of niacinamide employed will range in a weight ratio to caffeine between about 0.25 and about 1.50:1, depending upon the amount of caffeine present. That is, caffeine levels just above 2 percent by weight can be solubilized with about a 0.25:1 weight ratio of niacinamide to caffeine. However, as the level of caffeine increases, the requisite weight ratio of niacinamide to caffeine also increases up to a level of about 1.50:1 for caffeine levels of about 20 percent by weight. The weight ratios of

niacinamide effective for selected concentrations of caffeine are depicted below in Table I:

TABLE I

CAFFEINE WEIGHT PERCENT	WEIGHT RATIO NIACINAMIDE:CAFFEINE
2.5%	4:10 - 5:10
5.0%	7.5:10 - 8.5:10
7.5%	9.0:10 - 1.0:1.0
10.0%	1:1
12.5%	1.1:1.0 - 1.2:1.0
15.0%	1.2:1.0 - 1.25:1.0
17.5%	1.25:1.0 - 1.35:1
20.0%	1.35:1.0 - 1.45:1.0

Of course, greater levels of niacinamide can be employed up to a weight ratio to caffeine of 1.50:1. Preferred solutions have a level of caffeine between about 2.5 and about 5.0 percent by weight and a weight ratio of niacinamide to caffeine between about 0.40 and about 0.90:1. Even more preferred solutions contain a level of caffeine between about 2.75 and about 3.50 percent by weight and a weight ratio of niacinamide to caffeine of about 0.60:1.

The limited water solubility of nicotinic acid correspondingly reduces the amount of caffeine that can be solubilized with this co-solubilizer. Nicotinic acid can be dissolved in water up to a level of about 1.67 percent by weight. The maximum concentration can solubilize up to about 2.30 percent by weight of caffeine at pH 4.0.

Increasing the pH with an alkalizing agent increases the amount of nicotinic acid that can go into solution, which consequently

increases the amount of caffeine that can be solubilized. Greater than 6 percent by weight of nicotinic acid in solution requires a pH greater than desired levels. In addition, at higher concentrations, nicotinic acid is an undesirable rubifacient.

The caffeine solutions of the present invention are buffered to a pH less than about 6, and preferably less than about 5. Solutions containing aspartame are preferably buffered to a pH of about 4.3. The solutions may contain a mixture of niacinamide and nicotinic acid.

The buffering agent selected will depend upon the solution pH produced by the other ingredients. For solutions containing only caffeine, a co-solubilizing agent and optionally folic acid, a pH above 6 may result, that can be buffered below 6 with an acidulent such as citric acid, nicotinic acid, hydrochloric acid, ascorbic acid and the like. The preferred acidulents are nicotinic acid, citric acid and ascorbic acid. When strongly acidic ingredients such as ascorbic acid are used, a basic buffer may be needed. For example, when ascorbic acid is present at a level greater than about 1.30 percent by weight, a solution pH less than about 4.0 will result, necessitating the addition of a basic buffer such as sodium bicarbonate, sodium hydroxide, potassium hydroxide, potassium carbonate and the like. Essentially any alkalizing agent may be employed. Sodium hydroxide is the preferred basic buffer.

The amount of buffer employed should be that amount effective to produce the desired pH. That is, an amount effective to produce a pH less than about 6, and preferably an amount effective to produce a pH less than about 5. Solutions of the present invention buffered with citric acid will typically contain between about 0.10 and about 1.0 percent by weight of citric acid.

Preferred solutions in accordance with the present invention also contain folic acid to replace amounts of this essential B-vitamin believed to be depleted by caffeine. As noted above, the present invention incorporates the unexpected discovery that the caffeine solutions of the present invention increase the solubility of folic acid in water. Therefore, caffeine solutions in accordance with the present invention preferably contain the maximum amount of folic acid soluble therein, up to an amount effective to provide at least 50 percent of the minimum RDA of folic acid in a 4.0 mL quantity of caffeine solution.

The caffeine solutions of the present invention may optionally include other essential vitamins in the maximum quantity soluble up to an amount effective to provide the minimum RDA in a 2.5 mL quantity of solution. Such vitamins include ascorbic acid, A, D and E Vitamins, pyridoxine and thiamine and acid addition salts thereof, where applicable. Anti-allergens and stimulants may also be included, such as ginseng, epinephrine, ephedrine, pseudoephedrine, norephedrine, norepinephrine, and the like, and acid addition salts thereof. Dextromethorphan acid addition salts may also be included.

Ascorbic acid may also be employed as a buffer. However, the amount required to buffer a caffeine/niacinamide solution has little nutritional value, because of the strong acidity of ascorbic acid. When nutritional quantities of ascorbic acid are employed, it becomes necessary to buffer the solution with a basic buffer system.

The caffeine solutions of the present invention may contain an artificial sweetener and natural or artificial flavorings and agents to mask the taste of the caffeine, co-solubilizing agent and other ingredients. The artificial sweeteners to be used in the caffeine solutions of the invention can be any of those known for use in food

products. Examples include saccharin, cyclamate, acesulfame K, aspartame, alatame, and the like. The artificial sweetener will be present at a level between about 0.10 and about 2.0 percent by weight. The preferred artificial sweetener is aspartame at a level of between about 0.10 and about 1.0 percent by weight, and preferably at a level of about 1.0 percent by weight. One of ordinary skill in the art will appreciate that significant quantities of potent artificial sweeteners are being employed, thus illustrating the difficulties inherent in masking the taste of caffeine solutions.

Examples of suitable natural and artificial flavoring agents include vanillin, wintergreen, peppermint oil, orange oil, lemon oil, licorice, sassafras, natural and artificial cherry, natural vanilla extract, ethylene vanillin, coffee extract, chocolate extract, artificial chocolate flavoring, cocoa extract, and the like. The flavoring agents are typically oils that must be solubilized in the caffeine solutions of the present invention with an emulsifying system. Typically, a stock solution of flavoring agent oil in an emulsifier system is prepared that is then dispersed in the caffeine solutions of the present invention. Flavoring agent oils are preferably dissolved in a 50:50 blend of Tween 20 and Tween 80 at levels between about 10 and about 25 percent by weight, and preferably at a level of about 20 percent by weight. Between about 0.25 and about 10.0 percent by weight, and preferably between about 0.50 and about 1.50 percent by weight of this stock solution is then added to the caffeine solutions of the present invention. At higher concentrations of caffeine and the co-solubilizing agent, an amount of emulsifier at the lower end of the disclosed range is effective.

The caffeine solutions of the present invention may optionally further include an effective amount of an analgesic capable

of being topically absorbed through the skin or mucous membranes or an effective amount of a topical anesthetic capable of being absorbed through the skin or mucous membranes. Examples of suitable analgesics include acetyl salicylic acid, acetaminophen, ibuprofen, ketoprofen, menthol and the like. Such analgesics have been found to have increased water solubility in the caffeine solutions of the present invention. Thus, for example, solutions in accordance with the present invention containing a topically absorbed analgesic may include acetyl salicylic acid, i.e., aspirin, at levels up to about 10.0 percent by weight.

Topical anesthetics suitable for use with the present invention include procaine, lidocaine, benzocaine, holocaine, dibucaine, acid addition salts thereof, and the like. The topical anesthetics, especially the acid addition salts, have also been found to have increased water solubility in the caffeine solutions of the present invention. Thus, solutions in accordance with of the present invention containing a topical anesthetic may, for example, include procaine hyddrochloride at levels up to about 10.0 percent by weight. The caffeine solutions of the present invention optionally containing an analgesic or topical anesthetic are effective in the temporary relief of skin or mucous membrane inflammation, such as is associated with toothache, gum disease, Herpes infection, sore throat and the like.

The caffeine solutions of the present invention are prepared by dissolving the desired amount of caffeine, co-solubilizing agent, and the water-soluble optional ingredients such as folic acid, other vitamins and minerals, analgesic, topical anesthetic, etc., in water with stirring. Room temperature water may be employed, or the water may be heated to a temperature up to about 100°C to facilitate the dissolution of the ingredients.

The pH of the solution is measured and adjusted to the desired pH with an appropriate buffering agent. That is, an acidic buffering agent is used if the pH is high and is to be decreased, while a basic buffering agent is used if the pH is low and is to be increased. Once the pH of the caffeine solution is adjusted, the emulsifier system containing the water-insoluble ingredients is added. Typically, this is a 50:50 blend of Tween 20 and Tween 80 containing the flavoring agent oils.

After the pH is adjusted, and either before, during or after the flavoring agent oil-emulsifier system is added, the artificial sweetener may be added. Folic acid, when employed, must be added first, in the form of an alkali salt. The mixture is then stirred until a uniform, homogeneous solution is obtained. The resulting solution is then dispensed into containers by conventional means.

Thus, it can be appreciated that the present invention provides a concentrated oral caffeine dosage form without the objectionable taste heretofore associated with concentrated caffeine solutions. The following examples further illustrate the present invention, and are not to be construed as limiting the scope thereof. All parts and percentages are by weight unless expressly indicated to be otherwise, and all temperatures are in degrees Celsius. All chemicals were obtained from Amend Drug & Chemical of Irvington, New Jersey.

EXAMPLES

EXAMPLE 1

To 500 g of water was added with mixing 16 g caffeine, 9.8 g niacinamide and 20 mg folic acid. The ingredients dissolved rapidly, forming a uniform, homogeneous solution. The pH of the solution was adjusted to 4.3 with 0.7 g citric acid. 8.3 g of a mixture of 20 percent by weight of peppermint oil, 40 percent by weight of Tween 20 and 40 percent by weight of Tween 80 is then added to the solution with stirring, followed by 3.5 g aspartame and 1 mg of vanillin.

Stirring was continued until a uniform, homogeneous minty vanilla-flavored caffeine solution was obtained.

EXAMPLE 2

A caffeine solution was prepared as in Example 1 using 22 g niacinamide, 22 g caffeine, 40 mg folic acid and 8 g ascorbic acid. The same quantities of the flavoring agent oil emulsifier system, aspartame, vanillin and water were employed. The folic acid was added in the form of a 1 percent aqueous solution buffered to a pH greater than 10, with about 10 percent by weight of sodium hydroxide. Because of the acidity of the ascorbic acid, the pH of the solution was adjusted to 4.3 with 1.5 g of sodium hydroxide.

EXAMPLE 3

A caffeine solution was prepared as in Example 1 using 8 g niacinamide, 16.1 g caffeine, 1 g nicotinic acid, 8.8 g of the 1 percent folic acid mixture of Example 2, 5.4 g aspartame and 5.4 g of peppermint oil, emulsified as in Example 1. 500 g of water was employed. A minty-flavored solution was obtained containing 3.0 percent by weight of caffeine at a pH of 4.5.

EXAMPLE 4

A caffeine solution was prepared as in Example 1 based on 82.8 g of water, to which was added 1.8 g nicotinic acid, 3.0 g caffeine, 0.8 g of the 1 percent folic acid solution of Example 2, 1.6 g ascorbic acid, 1.0 g aspartame and 8.8 g of a flavoring agent oil emulsified as in Example 1, but substituting orange oil for peppermint oil. Because of the acidity of the ascorbic acid, the pH of the solution was adjusted to 4.5 with 0.2 g of sodium hydroxide. An orange-flavored solution containing 3.0 percent by weight of caffeine was obtained.

INDUSTRIAL APPLICABILITY

The caffeine solutions of the present invention are useful in the form of a breath spray or breath drops delivering about a 2.5 to 4.0 mL quantity of solution. However, the caffeine solutions of the present invention are also useful in the form of liquicaps, gum, candy such as lozenges or dark, milk or white chocolate-based candy.

The foregoing examples and description of the preferred embodiment should be taken as illustrating, rather than as limiting, the present invention as defined by the claims. As will be readily appreciated, numerous variations and combinations of the features set forth above can be utilized without departing from the present invention as set forth in the claims. All such modifications are intended to be included within the scope of the following claims.

WHAT IS CLAIMED IS:

1. An aqueous caffeine solution characterized by a co-solubilizing agent selected from the group consisting of niacinamide, nicotinic acid and mixtures thereof present at a level up to the maximum concentration soluble in water and in a weight ratio to said caffeine less than 1.50:1, characterized in that said caffeine is present up to the maximum level between about 2 and about 20 percent by weight that is water-soluble in combination with said co-solubilizing agent, and said solution is buffered to a pH less than about 6.

2 The caffeine solution of claim 1, characterized in that it is buffered to a pH less than about 5.

3. The caffeine solution of claim 2, characterized in that it is buffered to a pH of about 4.3.

4. The caffeine solution of claim 1, characterized in that said co-solubilizing agent is characterized by niacinamide being present in a weight ratio to caffeine between about 0.25 and about 1.50:1.

5. The caffeine solution of claim 1, characterized in that said co-solubilizing agent is nicotinic acid present in a level up to about 1.67 percent by weight and said caffeine is present at a level up to about 2.30 by weight.

6. The caffeine solution of claim 1, characterized in that it is buffered with an acidulent selected from the group consisting of citric acid, ascorbic acid, hydrochloric acid and nicotinic acid.

7. The caffeine solution of claim 1, characterized in that it is buffered with an alkalizing agent selected from the group consisting of sodium hydroxide, sodium bicarbonate, potassium hydroxide and potassium bicarbonate.

8. The caffeine solution of claim 1, further characterized by one or more essential vitamins at a level soluble in said caffeine solution up to an amount effective to provide the minimum Recommended Daily Allowance of said vitamin in a 4.0 mL quantity of said caffeine solution.

9. The caffeine solution of claim 8, characterized in that said vitamin is selected from the group consisting of ascorbic acid, folic acid, A, D and E vitamins, pyridoxine and thiamine.

10. The caffeine solution of claim 1, further characterized by an effective amount of an analgesic, topical anesthetic anti-allergen or stimulant capable of being effectively absorbed through the skin or mucus membrane.

11. The caffeine solution of claim 10, characterized by an analgesic selected from the group consisting of acetyl salicylic acid, acetaminophen, ibuprofen, ketoprofen and menthol.

12. The caffeine solution of claim 10, characterized by a topical anesthetic selected from the group consisting of procaine, lidocaine, benzocaine, holocaine, dibucaine and acid addition salts thereof.

13. The caffeine solution of claim 10, characterized by an anti-allergen or stimulant selected from the group consisting of ginseng, epinephrine, ephedrine, pseudoephedrine, norephedine, norepinephrine and the acid addition salts thereof.

14. The caffeine solution of claim 1, further characterized by an effective amount of an artificial sweetener selected from the group consisting of saccharin, cyclamate, acesulfame K, aspartame and alatame.

15. The caffeine solution of claim 14, characterized in that said artificial sweetener comprises aspartame at a level between about 0.10 and about 1.0 percent by weight.

16. The caffeine solution of claim 17, further characteized by one or more natural or artificial flavoring agents selected from the group consisting of vanillin, wintergreen, peppermint oil, orange oil, lemon oil, licorice, sassafras, natural and artificial cherry flavor, natural vanilla extract, ethylene vanillin, coffee extract, chocolate extract, artificial chocolate flavoring and cocoa extract.

17. A method for preparing an aqueous caffeine solution characterized by the steps of:

dissolving caffeine and a co-solubilizing agent selected from the group consisting of niacinamide, nicotinic acid and mixtures thereof in water, wherein said co-solubilizing agent is present at a level up to the maximum concentration soluble in water and in a weight ratio relative to caffeine less than 1.50:1, and said caffeine is present up to the maximum level between about 2 and about 20 percent by weight that is water-soluble in combination with said co-solubilizing agent; and

buffering said caffeine solution to pH less than about 6.

18. The method of claim 17, characterized in that said caffeine solution is buffered to a pH less than about 5.

19. The method of claim 18, characterized in that said caffeine solution is buffered to a pH of about 4.3.

20. The method of claim 17, characterized in that said co-solubilizing agent comprises niacinamide present in a weight ratio relative to caffeine between about 0.25 and about 1.50:1.

21. The method of claim 17, characterized in that said co-solubilizing agent is nicotinic acid present at a level up to about 1.67 percent by weight and said caffeine is present at a level up to about 2.30 percent by weight.

22. The method of claim 19, characterized in that said caffeine solution is buffered with an acidulent selected from the group consisting of citric acid, ascorbic acid, hydrochloric acid and nicotinic acid.

23. The method of claim 17, characterized in that said caffeine solution is buffered with an alkalizing agent selected from the group consisting of sodium hydroxide, sodium bicarbonate, potassium hydroxide and potassium bicarbonate.

24. The method of claim 17, further characterized by the step of dissolving in said caffeine solution, after said step of buffering said caffeine solution, an artificial sweetener selected from the group consisting of saccharin, cyclamate, acesulfame K, aspartame and alatame.

25. The method of claim 24, characterized in that said artificial sweetener comprises aspartame at a level between about 0.10 and about 1.0 percent by weight.

26. The method of claim 17, further characterized by the step of dispersing in said caffeine solution, after said buffering step, one or more emulsifiers in combination with one or more flavoring agent oils selected from the group consisting of vanillin, wintergreen, peppermint oil, orange oil, lemon oil, licorice, sassafras, natural and artificial cherry flavor, natural vanilla extract, ethylene vanillin, coffee extract, chocolate extract and cocoa extract.

27. The method of claim 17, characterized in that folic acid or ascorbic acid is dissolved with said caffeine and said

co-solubilizing agent in said water in an amount soluble therein up to an amount effective to provide the minimum Recommended Daily Allowance of said ascorbic acid or said folic acid in a 4.0 mL quantity of said caffeine solution.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/01218

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A01N 43/60, 43/40; A61K 31/495, 31/44
US CL :514/264, 356, 357

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/264, 356, 357

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Registry, HCPLUS, WPIDS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US, A, 4,076,856 (ZEITLIN ET AL.) 28 February 1978, see especially examples I and II.	1-6, 14-15 --- 7-13, 16-27
X --- Y	US, A, 3,829,569 (RICE) 13 August 1974, see entire document.	1-6, 10-11, 16 --- 7-9, 12-15, 17-27
X --- Y	WO, A, 87/01285 (BLASS) 12 March 1987, see pages 5-13, examples 7 and 9.	1-11, 14 --- 12-13, 15-27
X --- Y	Chemical Abstracts, Volume 87, issued 1995, Klosa, "Caffeine combination", abstract no. 87:106752, DE 2,559,384, 14 July 1977, 6 pages, see entire abstract.	1-6, 10 --- 7-9, 11-27

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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18 MARCH 1997	04 APR 1997
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/01218

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	WPIDS Abstracts, Volume 86, issued 1996, Budnikov et al., "Voltametric determn. of papaverine - involves dissolving of sample indi methyl formamide, adding tetra ethyl-ammonium and polarography", abstract no. 86-149192, SU 1,190,248, 07 November 1985, 6 pages, see entire abstract.	1-6, 10 ---------- 7-9, 11-27
X --- Y	WPIDS Abstracts, Volume 82, issued 1996, Salivanova et al., "Chromatographic analysis of pharmaceutical compsn. - useful in determn. of phenobarbital, diphenin, nicotinic acid, spasmolytic, glutamic acid, caffeine and glucose", abstract no. 82-13420E, SU 826,224, 30 April 1981, 3 pages, see entire abstract.	1-6, 10 ---------- 7-9, 11-27
X	Chemical Abstracts, Volume 107, issued 1996, Blass, "Therapeutic composition containing an analgesic nicotinamide, and NAD for treatment of symptoms associated with alcohol intake", abstract no. 107:54012, WO 87/01285, 12 March 1987, 30 pages, see entire abstract.	1-27